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EXAMINER	
RAWLINGS, STEPHEN L	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 08/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/031,158	PASTAN ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,10,15-20 and 24-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,10,15-20,24-28,34,35 and 45-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-6,10,15-20 and 24-54* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20020111*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *20040607*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed January 11, 2002 is acknowledged and has been entered in part. The amendment to page 53, as indicated, has not been entered; it appears that Applicant intended to amend page 59, not page 53. In order to expedite prosecution, a notice regarding the impropriety of the amendment has not be mailed; however, in reply to this Office action, Applicant is directed to again amend page 59, as intended by the amendment filed January 11, 2002.

2. As noted in the previous Office action mailed February 24, 2004, receipt of the amendment filed April 10, 2002 is acknowledged; however, contrary to that Office action, the amendment cannot be entered because the marked-up versions of claims 1-6 have been incorrectly numbered as 7-12. Applicant has noted the impropriety of the amendment filed February 24, 2002 at page 10 of the amendment filed March 17, 2004 and has submitted the latter amendment to replace the former amendment.

3. The amendment filed April 17, 2002 is acknowledged and has been entered.

4. The amendment filed March 17, 2004 is acknowledged and has been entered. Claims 7-9, 11-14, and 21-23 have been canceled. Claims 1-6, 10, 15-20, 24-36, and 40-44 have been amended. Claims 45-54 have been added.

5. Claims 1-6, 10, 15-20, and 24-54 are pending. Claims 29-33, 36-44, and 48-54 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

6. Claims 1-6, 10, 15-20, 24-28, 34, 35, and 45-47 are currently under prosecution.

Election/Restrictions

7. As agreed during the interview of March 16, 2004, because the restriction and election requirement set forth in the Office action mailed February 24, 2004 was made without consideration of a preliminary amendment, said restriction and election requirement has been vacated. A new restriction and election requirement is set forth below.

8. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1-6, 10, 15-20, 24-28, 34, 35, and 45-47, drawn to a polypeptide, a nucleic acid molecule encoding said polypeptide, a vector comprising said nucleic acid molecule, and a method for eliciting an immune response in a subject comprising administering to the subject a composition comprising said polypeptide.

Group II, claim(s) 20 and 30-33, insofar as the claims are drawn to a method for eliciting an immune response in a subject comprising administering to the subject a composition comprising a nucleic acid molecule.

Group III, claim(s) 20 and 29, insofar as the claims are drawn to a method for eliciting an immune response in a subject comprising administering to the subject a composition comprising an antigen presenting cell.

Group IV, claim(s) 36-42 and 48-54, drawn to a method for detecting cancer in a subject.

Group V, claim(s) 43, drawn to an antibody.

Group VI, claim(s) 44, insofar as the claim is drawn to a method for modulating levels of a protein in a cell comprising introducing into the cell a composition comprising a ribozyme.

Group VII, claim(s) 44, insofar as the claim is drawn to a method for modulating levels of a protein in a cell comprising introducing into the cell a composition comprising an antisense oligonucleotide.

Group VIII, claim(s) 44, insofar as the claim is drawn to a method for modulating levels of a protein in a cell comprising introducing into the cell a composition comprising a DNA binding protein.

Group IX, claim(s) 44, insofar as the claim is drawn to a method for modulating levels of a protein in a cell comprising introducing into the cell a composition comprising a nucleic acid molecule encoding a protein.

9. The inventions listed as Groups I-IX do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The special technical feature of group I is making and using a polypeptide.

The special technical feature of group II is administering to the subject a composition comprising a nucleic acid molecule.

The special technical feature of group III is administering to the subject a composition comprising an antigen presenting cell.

The special technical feature of group IV is detecting cancer in a subject.

The special technical feature of group V is making an antibody.

The special technical feature of group VI is introducing into the cell a composition comprising a ribozyme.

The special technical feature of group VII is introducing into the cell a composition comprising an antisense oligonucleotide.

The special technical feature of group VIII is introducing into the cell a composition comprising a DNA binding protein.

The special technical feature of group IX is introducing into the cell a composition comprising a nucleic acid molecule encoding a protein.

Accordingly, groups I-IX do not share the same or corresponding special technical feature so as to form a single general inventive concept under PCT Rules 13.1 and 13.2. In addition, PCT Rules 13.1 and 13.2 do not provide for a single general inventive concept to comprise more than the first mentioned product, the first mentioned method for making said product, and the first mentioned method for using said product.

10. During a telephone conversation with Susan Alpert Siegel, Ph.D. on June 7, 2004, a provisional election was made with traverse to prosecute the invention of group I, claims 1-6, 10, 15-20, 24-28, 34, 35, and 45-47. Affirmation of this election must be made by applicant in replying to this Office action. Claims 29-33, 36-44, and 48-54 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

11. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the

application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Priority

12. Applicant's claim under 35 USC § 120 for benefit of the earlier filing date of the PCT/US00/19039, filed July 12, 2000, which claims benefit of US Provisional Application No. 60/143,560, filed July 13, 1999, and of US Provisional Application No. 60/157,471, filed October 1, 1999, is acknowledged. However, the present claims are not entitled to the claimed benefit of the earlier filing dates of some, or all of these applications for the following reasons:

Claims 1-3, 6, 10, 15-17, 20, 24-28, 34, 35, and 47 are not entitled to the claimed benefit of the earlier filing date of PCT/US00/19039 because claim 1 is drawn to a variant of a polypeptide comprising an amino acid sequence set forth as SEQ ID NO: 14 *having a conservative substitution*, or an immunogenic fragment thereof, and PCT/US00/19039 provides an insufficient disclosure of the claimed invention to meet the enablement and written description requirements set forth under 35 USC § 112, first paragraph. In particular, as noted in the rejection below, while PCT/US00/19039 describes a variant of the polypeptide of SEQ ID NO: 14 as, for example, having an amino acid sequence that is at least 90% identical to SEQ ID NO: 14, PCT/US00/19039 fails to provide an adequate written description of a variant *having a conservative substitution*. For this reason, the effective filing date of claims 1-3, 6, 10, 15-17, 20, 24-28, 34, 35, and 47 is filing date of the instant application, namely January 11, 2002.

Claims 4 and 18 are not entitled to the claimed benefit of the earlier filing dates of either provisional application because claims 4 and 18 are drawn to polypeptide of claim 1, wherein the polypeptide is specifically recognized by an antibody that specifically recognizes the amino acid sequence as set forth as SEQ ID NO: 14, and a nucleic acid molecule encoding said polypeptide, respectively. Neither of the provisional applications provide adequate written support for a polypeptide that is specifically recognized by an antibody that specifically recognizes the amino acid sequence as set forth as SEQ ID NO: 14. For this reason, the effective filing date of claims 4 and 18 is filing date of PCT/US00/19039, filed July 12, 2000.

Claims 5 and 19 are not entitled to the claimed benefit of the earlier filing dates of either provisional application because claims 4 and 18 are drawn to polypeptide of claim 1, that when

processed and presented in the context of Major Histocompatibility Complex molecules, activates T lymphocytes against cells that express the polypeptide of SEQ ID NO: 14, and a nucleic acid molecule encoding said polypeptide, respectively. Neither of the provisional applications provide adequate written support for a polypeptide that when processed and presented in the context of Major Histocompatibility Complex molecules, activates T lymphocytes against cells that express the polypeptide of SEQ ID NO: 14. For this reason, the effective filing date of claims 5 and 19 is filing date of PCT/US00/19039, filed July 12, 2000.

Claims 45 and 46 are entitled are not entitled to the claimed benefit of US Provisional Application No. 60/143,560 because US Provisional Application No. 60/143,560 provides an insufficient disclosure of the claimed invention to meet the enablement and written description requirements set forth under 35 USC § 112, first paragraph. In particular, US Provisional Application No. 60/143,560 does not provide an adequate description of the amino acid sequence set forth as SEQ ID NO: 14, or of the polynucleotide sequence set forth as SEQ ID NO: 13 to enable one skilled in the art to make and use the claimed invention. The effective filing date of claims 45 and 46 is the filing date of US Provisional Application No. 60/157,471, filed October 1, 1999.

In addition, it is further noted that claims 1-3, 6, 10, 15-17, 20, 24-28, 34, 35, and 47 are not entitled to the claimed benefit of the earlier filing dates of either provisional application because claim 1 is drawn to polypeptide specifically recognized by an antibody that specifically recognizes the amino acid sequence as set forth as SEQ ID NO: 14, or because claim 1 is drawn to polypeptide that when processed and presented in the context of Major Histocompatibility Complex molecules, activates T lymphocytes against cells that express the polypeptide of SEQ ID NO: 14. Again, neither of the provisional applications provide adequate written support for a polypeptide that is specifically recognized by an antibody that specifically recognizes the amino acid sequence as set forth as SEQ ID NO: 14and neither of the provisional applications provide adequate written support for a polypeptide that when processed and presented in the context of Major Histocompatibility Complex molecules, activates T lymphocytes against cells that express the polypeptide of SEQ ID NO: 14.

Claim 28 is not entitled to are not entitled to the claimed benefit of the earlier filing dates of PCT/US00/19039 or of the provisional applications, since claim 28 is drawn to the method of

claim 20, further comprising co-administering to the subject an immune adjuvant *comprising* a non-specific immune adjuvant, a subcellular microbial product and fraction, a hapten, an immunogenic protein, an immunomodulatory, an interferon, a thymic hormone, or a colony stimulating factor. None of the prior applications describe an immune adjuvant *comprising* such adjuvants or factors, but rather describe the immune adjuvant as being one of those adjuvants or factors.

Information Disclosure Statement

13. The information disclosure filed January 11, 2002 has been considered. An initialed copy is enclosed.

Oath/Declaration

14. The declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. The oath or declaration is defective because: Non-initialed and/or non-dated alterations have been made to the declaration. See 37 CFR § 1.52(c).

Specification

15. The disclosure is objected to because the disclosure sequences appearing in the specification and/or drawings are not properly identified by sequence identifier in accordance with 37 C.F.R. 1.821(d). In this instance, sequences are depicted in Figure 14, which are not properly identified by sequence identification numbers. Sequence identifiers for sequences appearing in the drawings may appear in the Brief Description of the Drawings. Appropriate action correcting this deficiency is required.

16. The disclosure is objected to because the disclosure refers to embedded hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified. Reference to hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified is impermissible and therefore requires deletion.

Examples of such impermissible disclosures appear, for example, at page 47 (line 6) and page 59 (line 31).

The attempt to incorporate essential or non-essential subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP § 608.01(p), paragraph I regarding acceptable incorporation by reference.

17. The specification is objected to because the use of numerous improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Examples of such improperly demarcated trademarks include GenBank™ (page 13, line 10) and FastTrack™ (page 43, line 3).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

Claim Objections

18. Claim 34 is objected to because of following informality:

Claim 34 is objected to because of the misspelling of "lymphocytes" as "lymphocytess". Appropriate correction is required.

Claim Rejections - 35 USC § 112

19. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

20. Claims 26-28, 34, and 35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a new matter rejection.

Claim 26 recites, "wherein the subject is a female at risk for developing breast cancer". At page 12 of the amendment filed March 17, 2004, Applicant has asserted written support for the amended claim language can be found in the specification, for example, at page 28 (lines 19-21). The disclosure to which Applicant has referred provides a description of administering a composition to "women prophylactically to provide an immune defense in the event that a TARP-expressing breast cancer develops later". This disclosure, however, does not suggest administering to women at any particular risk; nor does it adequately describe a subpopulation of females at particular risk for developing breast cancer. Therefore, the specification, including the claims, as originally filed, does not appear to provide proper and sufficient written support for the instant claim language.

Claim 27 recites, "wherein the administered composition further comprises CD8+ cells that are sensitized with antigen presenting cells pulsed with [...] a variant [of a polypeptide comprising an epitope of the protein having an amino acid sequence as set forth as SEQ ID NO: 14". At page 12 of the amendment filed March 17, 2004, Applicant has asserted written support for the amended claim language can be found in the specification, for example, at page 31 (lines 26-31), page 7 (line 9), page 17 (line 35), and page 18 (lines 14-25). However, it appears that these disclosures merely provide written support for sensitizing antigen presenting cells with an epitope of the polypeptide of SEQ ID NO: 14, not with an epitope of a variant of the polypeptide. Therefore, the specification, including the claims, as originally filed, does not appear to provide proper and sufficient written support, since the specification does not describe antigen presenting cells pulsed with a variant of the polypeptide of SEQ ID NO: 14, which can be used to sensitize CD8+ cells before administering the cells to a subject.

Claim 28 recites "an immune adjuvant comprising a non-specific immune adjuvant, a subcellular microbial product and fraction, a hapten, an immunogenic protein, an immunomodulatory, an interferon, a thymic hormone, or a colony stimulating factor". At page 12 of the amendment filed March 17, 2004, Applicant has asserted written support for the amended claim language can be found in the originally filed claim. However, the originally claim 28 read:

> The method of claim 20, further comprising administering to the subject an immune adjuvant selected from non-specific immune adjuvants, subcellular microbial products and fractions, haptens, immunogenic proteins, immunomodulators, interferons, thymic hormones and colony stimulating factor.

This claim, as originally written, fails to provide a written description of an immunoadjuvant, which is a *composition* comprising one of members of the Markush group, since instead the claim described an immunoadjuvant that **is** one of the members of the Markush group. Therefore, the specification, including the claims, as originally filed, does not appear to provide proper and sufficient written support, since the specification does not describe "an immune adjuvant **comprising** a non-specific immune adjuvant, a subcellular microbial product and fraction, a hapten, an immunogenic protein, an immunomodulatory, an interferon, a thymic hormone, or a colony stimulating factor" (emboldened for emphasis).

Further regarding claim 28, as originally written, the claim fails to provide a written description of an immunoadjuvant, which is a *composition* comprising a subcellular microbial product **and** fraction, since instead the claim described an immunoadjuvant that is either a subcellular microbial product or a subcellular microbial fraction. Therefore, the specification, including the claims, as originally filed, does not appear to provide proper and sufficient written support, since the specification does not describe "a subcellular microbial product **and** fraction" (emboldened for emphasis).

Because the specification, including the claims, as originally filed, does not appear to provide proper and sufficient written support, the claim language appears to introduce new matter and thereby violates the written description requirement set forth under 35 USC § 112, first paragraph. However, these issues might be resolved if Applicant were to point to particular

disclosures in the specification, including the claims, as originally filed, which are believed to provide the necessary written support for the present claim language.

21. Claims 1-6, 10, 15-20, 24-28, 34, 35, and 47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a written description rejection.

Claims 1-3, 6, 10, 15-17, 20, 24-28, 34, 35, and 47 are directed to a genus of variants of the polypeptide of SEQ ID NO: 14, the members of which vary from the polypeptide of SEQ ID NO: 14 by at least a conservative substitution in their amino acid sequence relative to SEQ ID NO: 14. However, the specification provides only an adequate written description of the polypeptide of SEQ ID NO: 14, since the specification fails to describe the structural and functional features of at least a substantial number of the members of the claimed genus of variants, such that the skilled artisan could immediately envision, recognize, or distinguish at least a substantial number of those variants. For example, although the specification describes SEQ ID NO: 14, the specification fails to disclose the particularly identifying structural and functional features that are common to both the polypeptide of SEQ ID NO: 14 and the members of the genus of variants; so, the disclosure of SEQ ID NO: 14 cannot be regarded as descriptive, or representative of the genus of claimed variants. Moreover, the specification fails to describe which amino acids of the amino acid sequence set forth as SEQ ID NO: 14 can be replaced, and by which other amino acids, such that the resultant variant of the polypeptide of SEQ ID NO: 14 retains the structure and functional characteristics of the polypeptide of SEQ ID NO: 14. Accordingly, the instant written description of the claimed invention would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Claims 1, 4-6, 10, 15, 18, 19, 20, 24-28, 34, 35, and 47 are directed to a polypeptide that has an amino acid sequence that is at least 90% identical to the amino acid sequence set forth as SEQ ID NO: 14. However, again for the reasons set forth above, the specification provides only

an adequate written description of the polypeptide of SEQ ID NO: 14, since the specification fails to describe the structural and functional features of at least a substantial number of the members of the claimed genus of variants, such that the skilled artisan could immediately envision, recognize, or distinguish at least a substantial number of those variants. The instant written description of the claimed invention would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed, because Skolnick et al. (*Trends in Biotechnology* **18**: 34-39, 2000) discloses that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (see, e.g., the abstract; and page 34, *Sequence-based approaches to function prediction*). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see, in particular, the abstract and Box 2). Thus, even if a variant of the polypeptide of SEQ ID NO: 14 is specifically recognized by an antibody that binds specifically to the polypeptide of SEQ ID NO: 14 or which, when processed and presented in the context of MHC molecules, can elicit T lymphocyte-mediated immune response against cells expressing the polypeptide of SEQ ID NO: 14, one skilled in the art would not accept the assertion, which is actually based only upon an observed similarity in amino acid sequence, that such a variant of the polypeptide of SEQ ID NO: 14 is capable of functioning the same, or even as having the same structure as the polypeptide of SEQ ID NO: 14. Bowie et al. (*Science* **257**: 1306-1310, 1990) teaches that an amino acid sequence encodes a message that determines the shape and function of a protein; and, that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome. Bowie et al. teaches that the determination of protein structure from sequence data and, in turn, utilizing structural determinations to ascertain functional aspects of the protein is extremely complex (page 1306, column 1). Even if the skilled artisan were able to submit a complete list of the possible nucleic acids and the proteins encoded thereby, which fall within the scope of the claims, the skilled artisan could not recognize which of these would function similarly to a protein comprising SEQ ID NO: 14, and which would not.

Claims 1, 3, 6, 10, 15, 17, 20, 24-28, 34, 35, and 47 are directed to a polypeptide comprising an immunogenic fragment of the polypeptide of SEQ ID NO: 14 or a variant thereof. Generally, an immunogenic fragment may be as small as about 5 amino acids; therefore, the claims are drawn to a polypeptide comprising a very small portion of the amino acid sequence set forth as SEQ ID NO: 14 or a variant thereof. The claim encompasses polypeptides of markedly different structure and function, most of which have not been described by Applicant and many of which may not have been described by anyone, since the claims encompass polypeptides that have not yet been discovered. Accordingly, Applicant's disclosure would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Claims 27, 34, and 35 are further directed to a polypeptide comprising an epitope of the protein having the amino acid sequence set forth as SEQ ID NO: 14, or a variant thereof having a conservative substitution. However, the specification does not describe with any degree of particularity an epitope of the polypeptide of SEQ ID NO: 14, such that the specification might reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed; nor does it adequately describe members of the genus of polypeptides comprising an epitope of the protein having the amino acid sequence set forth as SEQ ID NO: 14. It follows then that the specification does not adequately describe a variant of such an epitope, or a variant of such a protein comprising such an epitope. As evidenced by Greenspan et al. (*Nature Biotechnology* **7**: 936-937, 1999), defining epitopes is not as easy as it seems. Greenspan et al. recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan et al., an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destablilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Thus, the epitope to which any given antibody or MHC molecule binds can only be identified empirically; and, absent a detailed and particular description of a representative number, or at least a substantial number of the members of the genus of epitopes of which the polypeptides and variants are

comprised, the skilled artisan could not immediately recognize or distinguish members of the genus of polypeptides and variants to which the claims are directed.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description'' Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). The *Guidelines* further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. Because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual

reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant had possession of the claimed invention at the time the application was filed.

It is noted that claims 1, 4, 5, 18, and 19 are directed to a genus of polypeptides that either are specifically recognized by an antibody that specifically recognizes a protein comprising SEQ ID NO: 14 or that, when processed and presented in the context of MHC molecules, activate T lymphocytes against cells expressing the protein of SEQ ID NO: 14. However, in deciding *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the Court held that a generic statement that defines a genus of nucleic acids *by only their functional activity* does not provide an adequate written description of the genus. By analogy and extension, a generic statement that defines a genus of variants by only the type of non-particular functional language of the present claims does not provide an adequate written description of the genus to which the claims are directed, since reciting that the members of the genus commonly function as an antigen capable of stimulating, or of being recognized by an immune system component specific for polypeptide of SEQ ID NO: 14 does not describe a specific and particular function of the variant that correlates with a specific and particular structural attribute also common to the members of the genus and to the polypeptide of SEQ ID NO: 14. The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

22. Claims 1-6, 10, 15-20, 24-28, 34, 35, and 45-47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject

matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The amount of guidance, direction, and exemplification set forth in the specification would not sufficient to enable the skilled artisan to make and use the claimed invention without first having to perform an undue amount of additional experimentation. Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). These factors include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The Nature of the Invention:

The invention, as claimed, is a polypeptide or a variant thereof , a nucleic acid molecule encoding said polypeptide or variant thereof, a vector comprising said nucleic acid molecule, and a method for using said polypeptide or variant thereof to elicit an immune response in a subject, which invention the specification asserts can be used as a target for intervention in the treatment of prostate cancer and TARP-expressing breast cancer, as well as a marker for cancer cells; see, e.g., page 28, lines 1-6.

The State of the Prior Art:

With regard to genetic or molecular diagnosis, following the discovery of a possible association between the expression of a gene or a product of that gene, and cancer, a long and arduous process must ensue by which it is determined if the over- or under-expression of the gene in cancer cells, relative to its normal level of expression in normal cells, can be used as a marker before the gene, its transcription product (e.g., an messenger RNA molecule), or its translation product (i.e., a protein encoded by the gene and its transcription product) can be used to diagnose or detect cancer. Sidransky (*Science* **278**: 1054-1058, 1997) teaches this process must first establish the reliability of a novel diagnostic method, which measures the expression

of a biomarker, through feasibility studies; then, after the reliability of the technique is established, its sensitivity and specificity must be assessed in formal clinical trials before the technique can be used with a reasonable expectation of success (page 1055, columns 1 and 2).

With regard to antitumor immunotherapy, Bodey et al. (*Anticancer Research* **20**: 2665-2676, 2000) teach, "while cancer vaccine trials have yielded tantalizing results, active immunotherapy has not yet become an established modality of anticancer therapy" (page 2665, column 2). As to the current state of the art, Bodey et al. comment, "the use of active specific immunotherapy (ASI) for cancer (cancer 'vaccines') is still in its scientific infancy despite several decades of clinical and basic research" (page 2668, column 2). Bodey et al. discloses, "ASI in at least one instance may have cured melanoma in a patient with metastatic disease, but that patient developed another immunologically and genetically distinct melanoma" (page 2668, column 2). In the abstract Bodey et al. speculate upon the reasons that ASI is ineffective or lacks efficacy:

> The theoretical basis for all of these approaches is very well founded. Animal models, albeit highly artificial, have yielded promising results. Clinical trials in humans, however, have been somewhat disappointing. Although general immune activation directed against the target antigens contained with a cancer vaccine has been documented in most cases, reduction in tumor load has not been frequently observed, and tumor progression and metastasis usually ensue, possibly following a slightly extended period of remission. The failure of cancer vaccines to fulfill their promise is due to the very relationship between host and tumor: through a natural selection process the host leads to the selective enrichment of clones of highly aggressive neoplastically transformed cells, which apparently are so dedifferentiated that they no longer express cancer cell specific molecules. Specific activation of the immune system in such cases only leads to lysis of the remaining cells expressing the particular TAAs [tumor associated antigens] in the context of the particular human leukocyte antigen (HLA) subclass and the necessary costimulatory molecules. The most dangerous clones of tumor cells however lack these features and thus the cancer vaccine is of little use.

The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. However, Ezzell (*Journal of NIH Research* **7**: 46-49, 1995) states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see the entire document, particularly last paragraph). Ezzell further teaches that no one is very optimistic that a single peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micro-metastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (page 48, paragraph 6). More recently, Bodey et al. (cited *supra*)

states, "there should be caution about assuming that a single epitope or even a few epitopes combined will be as effective 'crude' materials, which might better be thought of as 'polyvalent'" (page 2668, column 2). Spitler (*Cancer Biotherapy* **10**: 1-3, 1995) recognizes the lack of predictability of the nature of the art when she states, "ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: 'cancer vaccines don't work'. Ask a venture capitalist or the director of product development at a large pharmaceutical company and you're likely to get the same response" (page 1, paragraph 1).

Whatever avenue the artisan takes, in view of the unpredictability in the art, the rarity and lack of uniformity in the successful application, and the numerous and substantial limitations encountered, the threshold of enablement is high. The specification must enable one of skill in the art to make and to use the invention successfully without a need to first perform an undue amount of additional experimentation. To have success, the use of the invention must elicit a cancer-specific CTL response against the polypeptide of SEQ ID NO: 14 or a variant thereof. Boon (*Advances in Cancer Research*, 1992, **58**: 177-210) teaches that for successful application of active immunization in human patients, we have to stimulate immune defenses of organisms that have often carried a large tumor burden. Establishment of immune tolerance may therefore have already occurred in the patient and in such cases, active specific immunization will be fruitless, since anergic TCL cannot be activated, will not proliferate, and are deficient in effector function. Several lines of evidence suggest that large tumor burdens can tolerize, or at least depress the capability to respond against the tumor (page 206, paragraph 2).

There is considerable art indicating that cancer vaccines are ineffective, *even if antigen-specific T-lymphocytes can be activated by immunization protocols.* Lee et al. (*Journal of Immunology* **163**: 6292-6300, 1999) teaches, "although comparative ex vivo sensitization of pre- and postvaccination PBMC [peripheral blood mononuclear cells, such as B- and T-lymphocytes] has identified reproducible, vaccine-specific systemic T cell responses to immunization, in the majority of cases no regression is seen" (page 6292, column 1). In studies similar to those that are set forth in the examples in the specification, Lee et al. teaches that melanoma antigen epitopes were identified and that these peptide epitopes were capable of inducing highly specific T cell responses against autologous and some HLA-matched tumor cells. Lee et al. discloses, "these studies gave the impression that vaccines induce powerful immunizations comparable to

those demonstrable against common pathogens such as the influenza virus to which individuals are repeatedly exposed throughout their lifetime". However, "in most cases, this **vaccine-induced T cell reactivity still does not lead to tumor regression**" (emphasis added) (page 6299, column 1). One of the reasons for the discrepancy, Lee et al. suggest, may be that in vitro methods, which are commonly used to assess immune post-vaccination immune response, such as cell-mediated cytotoxicity assays, tend to "overestimate quantitatively the strength of the immune reaction within the organism" (page 6299, column 1). Lee et al. catalogs a variety of possible explanations for the lack of efficacy, including clonal deletion, exhaustion, or senescence, which are implicated in the development of systemic, epitope-specific immune tolerance, and inadequate immune response attributable to decreased T cell receptor signaling capacity or circulating immune-suppressive cytokines, but conclude that their data suggest that the extent rather than the quality of the response might be more significant limitation of the vaccination protocol (page 6299, column 2). More specifically, Lee et al. reports, "we were surprised at the relatively low numbers of CTL precursors after vaccination even in patients' samples that boasted an exceptional epitope-specific expansion in vitro" (page 6299, column 2). Lee et al. summarizes their study, teaching that "a peptide-based vaccine can effectively generate a quantifiable T cell-specific immune response in the PBMC of cancer patients, though such a response does not associate with a clinically evident regression of metastatic melanoma" (abstract). While Lee et al. refers specifically to the treatment of melanoma using a different epitope, the teachings are highly germane to the enablement issues relevant in the instant application, because the severe limitations will undoubtedly be shared by any protocol that uses the claimed invention, and there is no exemplification in the specification that would suggest otherwise. In yet another example, Zaks et al. (*Cancer Research* **58**: 4902-4908, 1998) teaches that immunization of patients diagnosed with cancer with a peptide epitope derived from the tumor antigen HER-2/neu/ErbB2 leads to activation of peptide-specific cytotoxic T-lymphocytes, but that the T-lymphocytes fail to recognize tumor cells that express the antigen. Zaks et al. discloses that their experience is not unique (page 4907, column 2). Gao et al. (*Journal of Immunotherapy* **23**: 643-653, 2000) found that although antitumor CTL response was enhanced by immunization, the tumors failed to regress. Gao et al. teaches that the lack of regression was associated with a lack of CTL migration to the tumor sites (abstract). Thus,

activation of peptide epitope-specific CTL is not an appropriate endpoint and a prediction or estimation of efficacy based only upon such data is imprudent or inexact.

Summarizing reasons for the lack of successful application of immunotherapy, Bodey et al. teaches that despite promising, even tantalizing results *in vitro* and *in vivo*, especially with animal models, the failure of cancer vaccines is predicated by very relationship between the tumor and the host immune system, which effectively makes the use of cancer vaccines futile:

> Malignant tumors undergo constant microevolution. Natural selection of the most advantageous surface IP [immunophenotype] involves constant modulation of previous IPs. Progressive dedifferentiation characterizes all neoplastically transformed cells. During this process, numerous 'novel' cell surface antigens appear, are modified and thus do not present the host's immune system with some immunogenic elements. The leukocytic inflammatory infiltrate contains cells with divers capabilities including neutrophils, macrophages and other professional APCs [antigen-presenting cells], as well as T lymphocytes. In situ activation of TAA [tumor-associated antigen] specific CTL [cytotoxic T-lymphocyte] clones occurs and thousands of tumor cells are lysed. However, as we would expect from any population in danger of extinction, the cells of the neoplastically transformed mass proceed with their microevolution and numerous clones of tumor cells survive each repeated attack by the immune system through secretion of immunoinhibitory cytokines, downregulation of MHC molecules, loss of costimulatory molecules, and induction of clonal T cell anergy, among other as yet uncovered ways. This process continues until the 'creation' (ironically as it may sound, by the host's immune system) of highly resistant, poorly immunogenic, and extremely aggressive clones of tumor cells. This is the reality of cancer progression: a back-and-forth struggle between host and tumor, with evolutionary dynamic exchanges throughout the entire process. Use of cancer vaccines to stimulate the immune system may be in vain" (citations omitted) (pages 2673-2674).

The Relative Skill of those in the Art:

Although high, the relative skill of those in the art is such that, absent a sufficient disclosure to enable the use of the claimed invention, an undue amount of additional experimentation would need be performed before the claimed invention, commensurate in scope with the claims, could be made and used to prevent, treat, or diagnose a disease, including cancer, and more particularly either breast or prostate cancer.

The Amount of Direction or Guidance Disclosed in the Specification:

The specification adequately describes the polypeptide of SEQ ID NO: 14; however, the specification does not adequately describe variants of this protein. The specification discloses that the protein is expressed in one particular prostate cancer cell line, which is not necessarily representative of other prostate cancer cell lines, prostate carcinomas, or other types of cancer.

In addition, the specification discloses the protein is expressed in breast cancer. The function of this protein is not disclosed and apparently remains unknown to this date.

Otherwise, the specification provides only a cursory review of the methodology that might be used to make and use the claimed invention, which does not extend beyond the conventional knowledge of the skilled artisan.

The Presence or Absence of Working Examples:

At pages 42-61, the specification discloses exemplification of the methodology that was used by Applicant to isolate and characterize a nucleic acid molecule encoding a protein, the discovery of which appears novel as of the earliest filing date sought by Applicant in the instant application. The specification further discloses exemplification of the methodology that was used by Applicant to characterize the protein, i.e., TARP, which is encoded by the isolated nucleic acid molecule, including the production of an antibody that binds specifically to the protein.

The specification, however, does not exemplify the isolation or production of variants of the protein encoded by the isolated nucleic acid molecule. Furthermore, the specification does not exemplify the use of the claimed invention to prevent, treat, or diagnose a disease, including diseases such as breast and prostate cancer.

Notably, the specification teaches the claimed polypeptide is not expressed in all types of cancer; see, e.g., page 56, lines 18-20. Thus, it is unreasonable to assert that the claimed invention provides a marker or target for such cancers.

The Predictability or Unpredictability of the Art:

As evidenced by the teachings of the references cited above to address the level of skill in the art and the state of the art, now and as of the earliest filing date sought by Applicant in the instant application, the art is characterized by high level of complexity, as well as unpredictability.

Moreover, as the claims are drawn to a genus of polypeptides, including the polypeptide of SEQ I DNO: 14 and variants thereof, it is noted that, with each and every discrepant nucleotide residue, the predictability that the claimed nucleic acid molecule will function

similarly enough to the isolated nucleic acid comprising SEQ ID NO: 14 for this instant disclosure to considered enabling declines significantly. As evidenced by the teachings of Bowie (cited *supra*) and Skolnick et al. (cited *supra*), even a single nucleotide alteration in the amino acid sequence of SEQ ID NO: 14 can drastically alter both the structure and function of the variant. Bowie et al. teaches that while it is known that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship and these regions can tolerate only conservative substitutions or none at all (page 1306, column 2). Burgess et al. (*Journal of Cell Biology* **111**: 2129-2138, 1990) exemplifies the sensitivity of proteins to alterations of even a single amino acid in a sequence. Burgess et al. teaches that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. As another example of this sensitivity to amino acid sequence variations, Lazar et al. (*Molecular and Cellular Biology*, 1988, **8**: 1247-1252) teaches that a replacement of aspartic acid at position 47 with alanine or asparagine in transforming growth factor alpha had no effect but that a replacement with serine or glutamic acid sharply reduced its biological activity. Thus, Lazar et al. teaches that even a single *conservative* type amino acid substitution may adversely affect the function of a protein.

The specification discloses that the claimed polypeptide is expressed by the prostate cancer cell line LNCaP, but not another prostate cancer cell line, namely PC3; see, e.g., page 55, lines 25-27. Wolfgang et al. (*Cancer Research* **61**: 8122-8216, 2001) also teaches the polypeptide of SEQ ID NO: 14, i.e., "TARP", is expressed in the androgen-sensitive LNCaP prostate cancer cell line, but not in the androgen-independent PC3 prostate cancer cell line; see, e.g., the abstract. On the basis of these results, because both cell lines may have accumulated mutations and epigenetic changes, such that one or both cell lines contain factors missing from the other, Wolfgang et al. teaches "it is not yet possible to establish the role of TARP in prostate cancer cell growth or normal growth" (page 8126, column 1). Thus, in the absence of exemplification that the claimed invention can be used as a target for intervention in the treatment of prostate cancer, as well as a marker for prostate cancer, the skilled artisan would not

accept the assertion that the claimed invention can be used as such without a need to first perform an undue amount of additional experimentation to establish the role of the claimed polypeptide in prostate cancer.

Regarding the possibility that the claimed invention provides a marker that might be diagnostically useful, Ward (*Developmental Oncology* 1985; **21**: 91-106) teaches not all markers can be reliably used in primary diagnosis. Ward teaches that a number of tumor-associated markers are, in fact, diagnostically unreliable. Rather, Ward teaches some markers are more useful as guides in monitoring the efficacy of treatment modules for malignant disease.

Regarding the possibility that the claimed invention might be therapeutically useful, the art of drug discovery for is highly unpredictable. With regard to anticancer drug discovery, for example, Gura (*Science* 1997; **278**: 1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile (abstract). Gura teaches that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models, but that only 39 have actually been shown to be useful for chemotherapy (page 1041, first and second paragraphs). Moreover, because of the lack of predictability in the art, Gura discloses that often researchers merely succeed in developing a therapeutic agent that is useful for treating the animal or cell that has been used as a model, but which is ineffective in humans, indicating that the results acquired during pre-clinical studies are often non-correlative with the results acquired during clinical trials (page 1041, column 2).

Additionally, to the extent that the claims are drawn to the use of an immunogenic fragment of the polypeptide of SEQ ID NO: 14, or a variant thereof, only certain immunogenic fragments might be expected to effectively induce antigen-specific cytotoxic T lymphocytes (CTL) that will kill target cells; other immunogenic fragments will not be effective. Lu et al. (*Cancer Research* **62**: 5807-5812, 2002), for example, teaches that four of five immunogenic fragments of prostate-specific membrane antigen (PSMA) were capable of inducing antigen-specific CTL killing of target cells, but only one was effective at recognizing prostate tumor cells expressing the protein; see, e.g., the abstract. These results are reminiscent of the teachings of Lee et al. (cited *supra*) and Zaks et al. (cited *supra*). Thus, while some immunogenic fragments may effective to stimulate a CTL-mediated response to the immunogenic fragment, the skilled

artisan cannot predict which immunogenic fragments might be used successfully to treat prostate cancer, or by analogy breast cancer.

The Breadth of the Claims:

Claims 1-3, 6, 10, 15-17, 20, 24-28, 34, 35, and 47 are directed to a genus of variants of the polypeptide of SEQ ID NO: 14, the members of which vary from the polypeptide of SEQ ID NO: 14 by at least a conservative substitution in their amino acid sequence relative to SEQ ID NO: 14.

The claims are further directed to a genus of polypeptides that comprise an amino acid sequence that is at least 90% identical to SEQ ID NO: 14.

The claims are still further directed to a genus of immunogenic fragments of the polypeptide of SEQ ID NO: 14, or of a variant of the polypeptide varying from the polypeptide of SEQ ID NO: 14 by at least a conservative substitution in their amino acid sequence relative to SEQ ID NO: 14.

Claims 20, 24-28, 34, and 35 are directed to the use of said genera of polypeptides to elicit an immune response in a genus of subjects diagnosed with a disease, or more particularly a cancer, namely prostate or breast cancer, or in a genus of female subjects at risk for a disease, or more particularly at risk for cancer, namely as breast cancer.

The Quantity of Experimentation Required:

As evidenced by the teachings of the references cited above to address the level of skill in the art and the state of the art, now and as of the earliest filing date sought by Applicant in the instant application, an undue amount of additional experimentation would have to be performed before the claimed invention, reasonably commensurate in scope with the claims, could be made and used successfully by the skilled artisan, since the skilled artisan cannot readily, that is, by routine experimentation alone, make variants of the polypeptide of SEQ ID NO: 14, nor use the polypeptide of SEQ ID NO: 14 or variants thereof to prevent, treat, or diagnose a disease, such as breast or prostate cancer.

Claims 1-3, 6, 10, 15-17, 20, 24-28, 34, 35, and 47 are directed to a genus of variants of the polypeptide of SEQ ID NO: 14, the members of which vary from the polypeptide of SEQ ID

NO: 14 by at least a conservative substitution in their amino acid sequence relative to SEQ ID NO: 14. Yet, the specification fails to describe which amino acids of the amino acid sequence set forth as SEQ ID NO: 14 can be replaced, and by which other amino acids, such that the resultant variant of the polypeptide of SEQ ID NO: 14 retains the structure and functional characteristics of the polypeptide of SEQ ID NO: 14. Because the specification fails to teach which amino acids of the amino acid sequence set forth as SEQ ID NO: 14 can be replaced, and by which other amino acids, such that the resultant variant of the polypeptide of SEQ ID NO: 14 retains the structure and functional characteristics of the polypeptide of SEQ ID NO: 14, the specification fails to provide a sufficient amount of guidance, direction, and exemplification to enable the skilled artisan to make the claimed invention without having to perform an undue amount of additional experimentation, since the skilled artisan would be left to determine the function and/or structure of the polypeptide of SEQ ID NO: 14, to then determine which amino acids of the amino acid sequence set forth as SEQ ID NO: 14 are critical to its function and/or structure, so as to recognize which amino acids can or cannot be replaced, and to finally determine by which other amino acids the critical and non-critical amino acids can be replaced, such that the resultant variant of the polypeptide of SEQ ID NO: 14 retains the structure and functional characteristics of the polypeptide of SEQ ID NO: 14.

Claims 1, 4-6, 10, 15, 18, 19, 20, 24-28, 34, 35, and 47 are directed to a polypeptide that has an amino acid sequence that is at least 90% identical to the amino acid sequence set forth as SEQ ID NO: 14. Yet, again for the reasons already discussed above, the specification fails to provide a sufficient amount of guidance, direction, and exemplification to enable the skilled artisan to make the claimed invention without having to perform an undue amount of additional experimentation.

Claims 1, 3, 6, 10, 15, 17, 20, 24-28, 34, 35, and 47 are directed to a polypeptide comprising an immunogenic fragment of the polypeptide of SEQ ID NO: 14 or a variant thereof. The claims are thus directed to a polypeptide comprising a very small portion of the amino acid sequence set forth as SEQ ID NO: 14 or a variant thereof. As many of the polypeptides encompassed by the claims have not been described by anyone, since many have not yet been discovered, Applicant's disclosure would not reasonably enable the skilled artisan to make at

least a reasonable number of the polypeptides without a need to first perform an undue amount of additional experimentation.

Claims 27, 34, and 35 are further directed to a polypeptide comprising an epitope of the protein having the amino acid sequence set forth as SEQ ID NO: 14, or a variant thereof having a conservative substitution. Yet, the specification does not describe with any degree of particularity an epitope of the polypeptide of SEQ ID NO: 14, such that the skilled artisan could make polypeptides comprising an epitope of the protein having the amino acid sequence set forth as SEQ ID NO: 14. Since, Greenspan et al. (cited *supra*) teaches defining epitopes is not as easy as it seems, an undue amount of additional experimentation would first have to be performed to characterize the epitopes of the polypeptide of SEQ ID NO: 14 of which the polypeptides of the claimed invention can be comprised before the invention can be made and used in accordance with Applicant's disclosure.

Further regarding the use of the claimed invention, the specification teaches the claimed invention can be used as a target for intervention in the treatment of prostate cancer and TARP-expressing breast cancer, as well as a marker for cancer cells; see, e.g., page 28, lines 1-6. Thus, the specification asserts that the claimed invention provides methods for treating prostate cancer and TARP-expressing breast cancers with immunotherapy; see, e.g., page 28, lines 5-8. The specification further asserts the invention can be used prophylactically to prevent breast cancer; see, e.g., page 28, lines 19-21. However, as evidence by the references cited herein, the amount of guidance, direction, and exemplification disclosed by Applicant is not reasonably commensurate in scope with the claims and would not be sufficient to enable the skilled artisan to use the claimed invention as described and/or claimed.

Were the polypeptide found to have potential as a therapeutic, it is again noted that while some immunogenic fragments may effective to stimulate a CTL-mediated response to the immunogenic fragment, the skilled artisan cannot predict which immunogenic fragments might be used successfully to treat prostate cancer, or by analogy breast cancer. Therefore, for this reason in addition to all of the above reasons, the skilled artisan could not use the claimed invention to treat or prevent cancer, including prostate and breast cancer, without the need to first perform an undue amount of additional experimentation.

Regarding the diagnostic use of the claimed invention, Tockman et al. (*Cancer Research* 1992; **52**: 2711s-2718s), for example, teaches many considerations that must be made in bringing a candidate tumor marker to successful clinical application; given only the benefit of Applicants' present disclosure, the skilled artisan could not use the claimed invention without having to perform an undue amount of additional experimentation. Critchfield (*Disease Markers* **15**: 108-111, 1999) teaches: "Indeed, to truly benefit society, the clinical value of the gene must be established" (page 109, column 1). Following the discovery of a novel gene Critchfield discusses the lengthy process that is involved in determining its usefulness as a biomarker for diagnosis; and in view of Critchfield, given only the benefit of Applicant's present disclosure of the invention, it is apparent the skilled artisan could not immediately use the claimed invention as a diagnostic marker without having to perform an undue amount of additional experimentation.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with *Ex parte Forman*, 230 USPQ 546 (BPAI 1986), the amount of guidance, direction, and exemplification disclosed by Applicant is not deemed sufficient to enable the skilled artisan to use the claimed invention without a need to perform an undue amount of additional experimentation.

23. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

24. Claims 1, 5, 6, 10, 15, 20, 24-28, 34, 35, and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 5, 6, 10, 15, 20, 24-28, 34, 35, and 47 are indefinite because claims 1 and 5 recite "the protein encoded by the amino acid sequence set forth as SEQ ID NO: 14" and "the protein encoded by the amino acid sequence as set forth as SEQ ID NO: 14", respectively. A protein is not encoded by an amino acid sequence, since a protein is comprised of an amino acid sequence and encoded by a nucleic acid sequence. Therefore, the metes and bounds of the claimed invention cannot be determined.

Claims 18 and 19 are indefinite because both claims depend from now canceled claim 12. Therefore, the metes and bounds of the claimed invention cannot be determined.

Claim Rejections - 35 USC § 102

25. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

26. Claims 1-3, 6, 10, 15-17, 20, 24, 25, 27, 28, and 47 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 01/04309 A1.

Claims 1-3, 6, 10, 15-17, 20, 24, 25, 27, 28, and 47 are given the effective filing date of the instant application, namely January 11, 2002, since PCT/US/00/19039 fails to provide an enabling disclosure of a variant of SEQ ID NO: 14 having a conservative substitution.

Claims 1-3, 6, 10, 15-17, 20, 24, 25, 27, 28, and 47 are drawn to a polypeptide, or an immunogenic fragment thereof, comprising SEQ ID NO: 14, a variant of said polypeptide, or an immunogenic fragment thereof, comprising an amino acid sequence that is at least 90% identical to SEQ ID NO: 14, a composition comprising said polypeptide or variant thereof, a nucleic acid molecule encoding said polypeptide or variant thereof, which may be operably linked to a promoter, a vector comprising said nucleic acid molecule operably linked to a promoter, and a method for eliciting an immune response in a subject comprising administering to a subject said polypeptide or variant thereof.

WO 01/04309 A1 (Pastan et al.) teaches a polypeptide comprising SEQ ID NO: 14; see, e.g., page 24, lines 1 and 2. In addition, Pastan et al. teaches polypeptides having an amino acid sequence that is at least 90% identical to SEQ ID NO: 14, which bind to antibodies raised against the polypeptide of SEQ ID NO: 14; see, e.g., page 24, lines 3-20. Pastan et al. teaches the polypeptide or variant thereof can be specifically recognized by an antibody that specifically recognizes the polypeptide of SEQ ID NO: 14, or, when processed and presented in the context of MHC molecules, can activate T lymphocytes against cells that express the polypeptide of SEQ ID NO: 14; see, e.g., page 5, lines 4-12. Pastan et al. teaches a composition comprising said polypeptide or variant thereof and a pharmaceutically acceptable carrier can be administered to a subject who suffers from prostate or breast cancer, or who has not been diagnosed with breast cancer; see, e.g., page 5, lines 32-34. Pastan et al. teaches the adminstration can elicit an immune response; see, e.g., page 41, lines 25-28. Pastan et al. teaches co-administering an immune adjuvant selected from, for example, non-specific immune adjuvants; see, e.g., page 6, liens 5-8. Pastan et al. teaches further administering CD8+ cells that have been sensitized in vitro to an epitope of the polypeptide of SEQ ID NO: 14; see, e.g., page 6, liens 1-4. Pastan et al. teaches vectors comprising a nucleic acid molecule encoding said polypeptide or variant thereof, which is operably linked to a promoter; see, e.g., page 26, lines 8, through page 27, line 16.

27. Claims 1-6, 10, 15-20, 28, and 47 are rejected under 35 U.S.C. 102(b) as being anticipated by Wolfgang et al. (*Proc. Natl. Acad. Sci. USA* **97**: 9437-9442, 2000).

Claims 1-6, 10, 15-20, 28, and 47 are given the effective filing date of the instant application, namely January 11, 2002, since PCT/US/00/19039 fails to provide an enabling disclosure of a variant of SEQ ID NO: 14 having a conservative substitution.

Claims 1-6, 10, 15-20, 28, and 47 are drawn to a polypeptide comprising SEQ ID NO: 14, a composition comprising said polypeptide, a nucleic acid molecule encoding said polypeptide, which is be operably linked to a promoter, a vector comprising said nucleic acid molecule operably linked to a promoter, and a method for eliciting an immune response in a subject comprising administering to a subject said polypeptide.

Wolfgang et al. teaches a polypeptide comprising SEQ ID NO: 14; see the entire document, particularly page 9438, Figure 1B. Because the polypeptide of Wolfgang et al. is the

polypeptide of SEQ ID NO: 14, the polypeptide of Wolfgang et al. comprises an immunogenic fragment of the amino acid sequence set forth as SEQ ID NO: 14. Furthermore, because the polypeptide of Wolfgang et al. is the polypeptide of SEQ ID NO: 14, the polypeptide of Wolfgang et al. is specifically recognized by an antibody that specifically recognizes the amino acid sequence as set forth as SEQ ID NO: 14 and that, when processed and presented in the context of Major Histocompatibility Complex molecules, activates T lymphocytes against cells that express the polypeptide of SEQ ID NO: 14. Wolfgang et al. teaches administering a composition comprising said polypeptide, an immune adjuvant, which is a subcellular microbial product (i.e., *Pseudomonas* exotoxin), and an pharmaceutically acceptable carrier to a subject to elicit an immune response; see, e.g., page 9438, column 2. Wolfgang et al. teaches a vector comprising a nucleic acid molecule encoding said polypeptide, which is operably linked to a promoter; see, e.g., page 9438, column 1.

28. Claims 1-3, 6, 10, 15-17, 20, 24, 28, and 47 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent Application Publication No. 2003/0108963 A1.

Claims 1-3, 6, 10, 15-17, 20, 24, 28, and 47 are given the effective filing date of the instant application, namely January 11, 2002, since PCT/US/00/19039 fails to provide an enabling disclosure of a variant of SEQ ID NO: 14 having a conservative substitution.

US Patent Application Publication No. 2003/0108963 A1 (Schlegel et al.) teaches a polypeptide comprising SEQ ID NO: 14; see the entire document (e.g., SEQ ID NO: 405 of the sequence listing). Schlegel et al. teaches a nucleic acid molecule comprising a polynucleotide sequence encoding the polypeptide; see, e.g., SEQ ID NO: 404 of the sequence listing. Schlegel et al. teaches a variant of the polypeptide, which comprises an amino acid sequence that is at least 90% identical to the amino acid sequence of the polypeptide; see, e.g., page 25, paragraph [0150]. Schlegel et al. teaches a variant of the polypeptide comprising a conservative amino acid substitution; see, e.g., page 25, paragraph [0151]. Schlegel et al. teaches a polypeptide comprising an immunogenic fragment of the polypeptide; see, e.g., page 20, paragraph [0089]; page 27, paragraph [0163]. Schlegel et al. teaches a vector comprising the nucleic acid molecule encoding the polypeptide, which is operably linked to a promoter; see, e.g., page 32, paragraph [0198], through page 34, paragraph [0213]. Schlegel et al. et al. teaches a vector comprising a

nucleic acid molecule encoding an immunogenic fragment of the polypeptide; see, e.g., page 20, paragraph [0106]. Schlegel et al. teaches a method for inducing an immune response comprising administering to a subject a composition comprising the polypeptide or an immunogenic fragment thereof and a pharmaceutically acceptable carrier; see, e.g., page 27, paragraph [0163]; page 30, paragraph [0181] through paragraph [0184]; page 35, paragraph [0219]. Schlegel et al. teaches the composition can comprise an immunoadjuvant and/or an immunomodulatory; see, e.g., page 30, paragraph [0182]; page 40, paragraph [0256]. Schlegel et al. teaches a pharmaceutical composition, which can be administered to a subject diagnosed with prostate cancer; see, e.g., page 40, paragraph [0256].

Conclusion

29. No claims are allowed.

30. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

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